REMARKS

This Response is submitted in reply to the non-final Office Action mailed on November 26, 2007. No fee is due in connection with this Response. The Director is authorized to charge any fees that may be required, or to credit any overpayment to Deposit Account No. 02-1818. If such a withdrawal is made, please indicate the Attorney Docket No. 112713-983 on the account statement.

Claims 1, 3-11, 19-21 and 23-53 are currently pending in this application. Claims 2, 12-18, 22 and 54-120 were previously canceled. In the Office Action, Claims 1, 3-11, 19-21 and 23-53 are rejected under 35 U.S.C. §103. For at least the reasons set forth below, Applicants respectfully submit that the rejections should be withdrawn.

Claims 1, 3-11, 19-21, 23-34 and 48-53 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,935,847 to Smith et al. ("*Smith*") in view of either U.S. Patent No. 6,759,245 to Toner et al. ("*Toner*") or U.S. Patent No. 5,912,177 to Turner ("*Turner*") and further in view of U.S. Patent No. 5,686304 to Codner ("*Codner*"). Claims 36-47 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Smith* in view of *Toner/Turner* and *Codner* in further view of U.S. Patent No. 5,989,215 to Delmotte ("*Delmotte*"). Applicants respectfully disagree with and traverse these alleged rejections for at least the reasons set forth below.

Independent Claims 1, 48 and 51 recite, in part, a closed supporting container comprising an interior surface comprising an ethylene vinyl acetate copolymer. In an embodiment, the present claims provide an in vitro cell culture employing a fibrin network in a flexible container. Applicants have surprisingly found that providing the flexible container with an interior surface of a portion of the side walls constructed from an ethylene vinyl acetate copolymer having a fibrin matrix presents an environment conducive to adherent cell proliferation and maturation. This allows for an improved flexible, gas permeable container in accordance with embodiments of the present claims that is suitable for culturing anchorage dependent mammalian cells for expansion and transplantation, which has previously been done using rigid, gas impermeable cell culture flasks or plates. In contrast, Applicants respectfully submit that the cited references are deficient with respect to the present claims.

Applicants respectfully submit that the skilled artisan would have no reason to combine the cited references to arrive at the claimed invention because the cited references have different modes of operation that teach away from each other and/or the present claims. For example, references must be considered as a whole and those portions teaching against or away from each other and/or the claimed invention must be considered. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve Inc.*, 796 F.2d 443 (Fed. Cir. 1986). "A prior art reference may be considered to teach away when a person of ordinary skill, upon reading the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the Applicant." *Monarch Knitting Machinery Corp. v. Fukuhara Industrial Trading Co., Ltd.*, 139 F.3d 1009 (Fed. Cir. 1998), quoting, *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994).

Smith is entirely directed to a multi-layer, flexible, gas-permeable container. See, *Smith*, column 2, lines 24-32. In fact, the outer walls that make up the container of *Smith* are made of the flexible, gas-permeable materials. In contrast to *Smith*, *Toner* is entirely directed to a modular cell culturing device including one or more two-compartment cartridge entirely comprising rigid and impermeable exterior walls 50, which explicitly teaches away from *Smith's* flexible, gas-permeable container. See *Toner*, column 2, lines 39-45, column 7, lines 38-59, column 11, lines 27-41 ("rigid impermeable walls 50"). In fact, the rigid walls of the cartridges are specifically intended and designed for being impermeable to liquids and gases to adequately maintain the bioreactor. See *Toner*, column 7, lines 54-63.

Toner also teaches a polymeric membrane 30 (which may be coated with fibrin) that separates a liquid compartment and an oxygenated fluid compartment of the cartridge. Nevertheless, *Toner* teaching using fibrin as a coating matter, which is already known in the art. Ignoring other teaching away aspects of *Toner* is a strong indication that the Patent Office is using Applicants' disclosure as a blueprint to pick and choose from isolated portions of the prior art in order to deprecate Applicants' claims. Such conduct is exemplary of hindsighted reasoning, which is clearly improper. Moreover, *Toner's* use of fibrin is specific to his device. For example, *Toner* does not coat the rigid walls of the cartridges, but the intermediate separating membrane within the cartridge. As a result, the cells growth takes place on the intermediate membrane and not on the interior of the outer walls.

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). This certainly applies here where one of the cited references is directed to a flexible, gas-permeable container (*Smith*) and the other cited reference is directed to a cartridge entirely comprising a rigid and impermeable exterior walls (*Toner*). As a result, the principle of operation for each device is important and specific to that particular device. The Patent Office has provided no evidence that the device of *Smith* works as modified by *Toner* and vice versa. Moreover, because of these differences, one skilled in the art would have no reason to modify or combine *Toner* and *Smith* to arrive at the present claims.

Certain cited references also explicitly teach away from the present claims. For example, *Toner* is entirely directed to an open or flow-through cell-culturing device (see *Toner*, column 2, lines 35-50), which teaches away from a closed container as recited in the present claims. *Toner's* cartridge includes oxygenated fluid inlet/out 3,3' and liquid inlet/outlet 5,5'. The inlets and outlets permit continuous fluid flow through *Toner's* cartridge. The inlets and outlets fulfill an objective of *Toner*, which is to cultivate cells on membrane 30 by passing flowing fluid along each side of the membrane 30. See *Toner*, column 2, lines 35-45. Accordingly, *Toner's* flow-through cartridge is an open system, not a closed system.

Delmotte teaches away from the present claims and a combination with *Smith* and *Toner*. *Delmotte* discloses a fibrin delivery device 10 having first and second syringes 12, 14 and a spray unit 18. A pressurizer 22 travels through each syringe 12, 14 to push fluid present in each syringe through the spray unit 18. *Delmotte*, column 8, lines 31-43, column 9, lines 47-58, Figures 1 and 4. One of ordinary skill in the art would recognize that syringes 12, 14 are rigid in order to withstand the pressure imposed by pressurizer 22 when pushing fluid out of each syringe. Accordingly, *Delmotte* teaches away from a closed support container having flexible and gas permeable exterior sidewalls in accordance with the present claims. Moreover, *Delmotte's* rigid syringes teach away from the flexible container of *Smith* and the modular cell culturing device of *Toner*.

Applicants also respectfully submit that, even if combinable, the cited references do not disclose or suggest every element of independent Claims 1, 48 and 51. For example, *Smith* fails

to disclose or suggest a closed supporting container comprising an interior surface comprising an ethylene vinyl acetate copolymer as required, in part, by Claims 1, 48 and 51.

The Patent Office alleges that it is not entirely clearly if the inner surface of *Smith's* container comprises an ethylene vinyl acetate copolymer. Applicants respectfully disagree and submit that it is completely clear that *Smith* is directed to an interior cell growth layer composed of polystyrene and exterior layer composed of a polymeric layer comprising a multiple component polymer alloy blend. For example, *Smith* teaches that the first layer of the films forms an inner cell growth surface. See *Smith*, column 3, line 59 to column 4, line 10. *Smith* teaches that the first layer is an ultra-thin layer of polystyrene. *Id.* *Smith* never discloses using ethylene vinyl acetate copolymer as any part of the inner cell growth surface layer. Moreover, *Smith* explicitly teaches away from an interior surface comprising an ethylene vinyl acetate copolymer by stating:

> While EVA [ethylene vinyl acetate] can hold an electrostatic charge, the charge has the undesirable tendency to decay over time. Eventually, the decay of the charge on EVA will render the container ineffective for growing adherent cells. Rigid styrene flasks with an electrostatic charge are known, and show less of a tendency to lose charge over time.
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> See *Smith*, column 2, lines 7-12 (emphasis added).

Accordingly, *Smith* fails to disclose or suggest a closed supporting container comprising an interior surface comprising an ethylene vinyl acetate copolymer in accordance with the present claims.

Toner, *Turner*, *Codner* and *Delmotte* fail to remedy the deficiencies of *Smith*. For example, *Toner* fails to disclose or suggest a closed supporting container comprising an interior surface comprising an ethylene vinyl acetate copolymer as required, in part, by Claims 1, 48 and 51. As previously discussed, *Toner* is relied upon only for the teaching that a fibrin matrix may be used to accommodate cell growth.

Turner fails to disclose or suggest a closed supporting container comprising an interior surface comprising an ethylene vinyl acetate copolymer as required, in part, by Claims 1, 48 and 51. *Turner* is directed to a system for selectively immobilizing stem cells that comprises combining a substrate having a coating comprising a fibrin matrix together with a substance capable of binding to the fibrin matrix and having a binding site for binding an RGD amino acid

sequence for binding to the stem cells. *Turner* fails to even disclose or suggest the use of and ethylene vinyl acetate copolymer anywhere in his disclosure.

Codner fails to disclose or suggest a closed supporting container comprising an interior surface comprising an ethylene vinyl acetate copolymer as required, in part, by Claims 1, 48 and 51. *Codner* is directed to cell culture apparatus formed of a plurality of thin (e.g., 0.005" or less), spaced, gas-permeable, silicone membranes sealed at their edges to form a bag-like vessel comprising one or more interior chambers suitable for containing cell culture media. See *Codner*, column 2, lines 66 to column 3, line 8. A suitable portion of the membrane surfaces are of suitable thickness and surface area to provide structural integrity to the apparatus and sufficient gas permeability for cell growth within the chamber. Nevertheless, *Codner* fails to even disclose or suggest the use of fibrin for growing cells anywhere in his disclosure, especially in a container having an inner layer of an ethylene vinyl acetate copolymer.

Delmotte fails to disclose or suggest a closed supporting container comprising an interior surface comprising an ethylene vinyl acetate copolymer as required, in part, by Claims 1, 48 and 51. Instead, *Delmotte's* is directed to rigid syringes as a medical delivery device. *Delmotte* fails to even disclose or suggest the use of ethylene vinyl acetate copolymer anywhere in his disclosure.

In sum, *Smith*, *Toner*, *Turner, Codner* and *Delmotte* fail to disclose or suggest any closed supporting container comprising an interior surface of an ethylene vinyl acetate copolymer. Moreover, the cited references fail to even recognize the advantages, benefits and/or properties of a fibrin matrix layer on a portion of an interior surface composed of an ethylene vinyl acetate copolymer in accordance with the present claims and provide no reasonable expectation of success with respect to same. For at least the reasons discussed above, the combinations of *Smith*, *Toner*, *Turner, Codner* and *Delmotte* are improper and do not teach, suggest, or even disclose all of the elements of independent Claims 1, 48 and 51 and the claims that depend from Claims 1, 48 and 51, and thus, fail to render the claimed subject matter obvious.

Accordingly, Applicants respectfully request that the obviousness rejections with respect to Claims 1, 3-11, 19-21 and 23-53 be reconsidered and the rejections be withdrawn.

For the foregoing reasons, Applicants respectfully request reconsideration of the above-identified patent application and earnestly solicit an early allowance of same. In the event there remains any impediment to allowance of the claims that could be clarified in a telephonic

interview, the Examiner is respectfully requested to initiate such an interview with the undersigned.

Respectfully submitted,

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